



Optimizing follow-up after Adult Granulosa Cell Tumor

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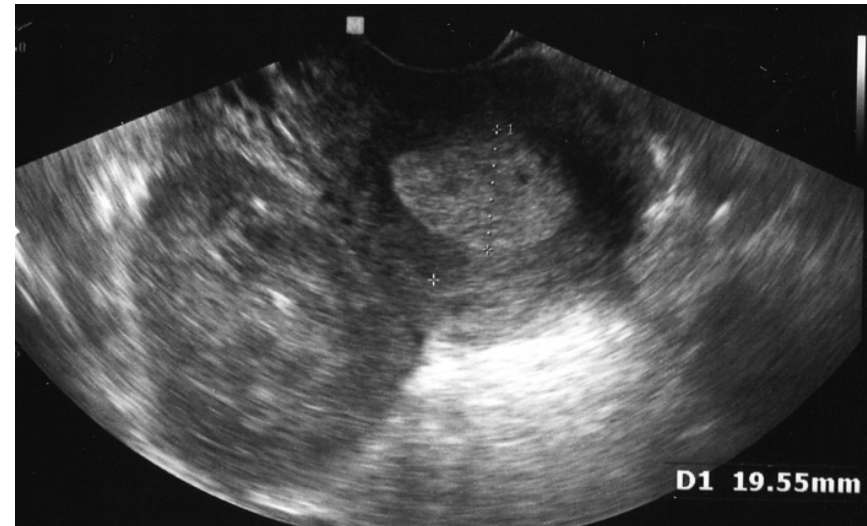
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No conflicts of interest



Adult-type GCT (AGCT)

- Incidence; 0.5-1.6/100 000
(Shumer & Cannistra 2003, Unkila-Kallio et al. 1998)
- Diagnosis; age 54 years
- Hormonally active: Produces E2, Inhibins
- Symptoms
 - 45% Abnormal vag. bleeding (Em pathology in 60%)
 - 25% Abdominal pain
 - 14% Abdominal distention
 - 14% No symptoms
- Signs; Unilateral ovarian solid mass
 - Thick endometrium
- 90% Stage I



AGCT – pathogenesis

Somatic point mutation in transcription factor FOXL2 (402C->G) (*Shah et al, 2009*)

- Present in 90-97% of AGCTs (*Shah et al 2009, Jamieson 2010*)
- Normal FOXL2; gonadal differentiation; Granulosa cells -> Sertoli-like cells (*Uhlenhaut et al 2009*)
- FOXL2 402C->G mutation;
 - Post-translational modifications (*Kim et al 2014*)
 - Impaired interaction with co-factors
 - Differential expression of genes regulating TGFβ pathway and hormone production (*Rosario et al 2014*)
 - Increased proliferation and decreased apoptosis (*Kim et al 2010*)

Follow-up after AGCT

1. Rationale of follow-up?
2. Identifying an increased risk of relapse
 - Correct diagnosis !
 - Prognostic factors
 - Clinical
 - Molecular
3. Performing Clinical follow-up
 - Follow-up patterns
 - Blood samples

Why follow-up?

Aiming for

1. Improved overall survival
2. No increased morbidity
3. Quality of life

In epithelial ovarian cancers (EOC)

- Serum marker surveillance has not improved survival in epithelial ovarian cancers (EOC)
- Early chemotherapy based on follow-up increased morbidity and decreased quality of life (*Rusdin et al, 2010*)

BUT; AGCT is not EOC!

- **AGCT surgical treatment is often feasible in the relapse; 71-85% optimal surgery at relapse (*Ertas et al, 2014*)**
- **Increased chances of complete removal of the local recurrent tumor if detected early (*Fleming et al, 2011*)**
- **Complete removal of relapse associated with increased survival in AGCT (*Mangilil et al, 2013*)**

Who to follow-up?

1. Most early stage → 25% risk of relapse
2. Higher risk in some patients
 - Identification/prognostic factors
 - Careful follow-up of the high-risk patients
 - Avoiding unnecessary examinations and worry in low-risk disease

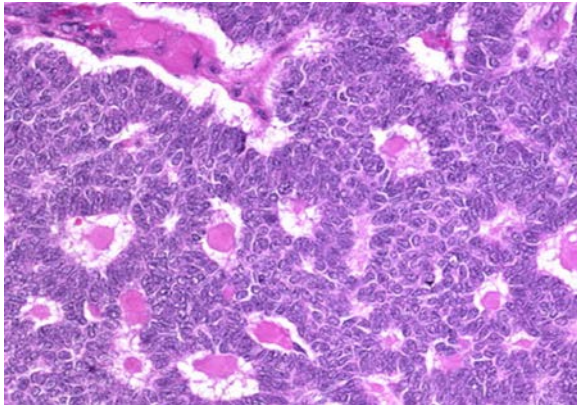
Stage (FIGO 2009)		
Stage I	218	(85.2%)
I	11	(4.3%)
Ia	130	(50.8%)
Ib	4	(1.6%)
Ic	73	(28.5%)
Stage II	23	(9.0%)
Stage III	10	(3.9%)

	Stage 1a	Stage 1c	Total
Finland			
50+	13.0%	36.7%	20.5%
50-	36.4%	52.4%	42.1%

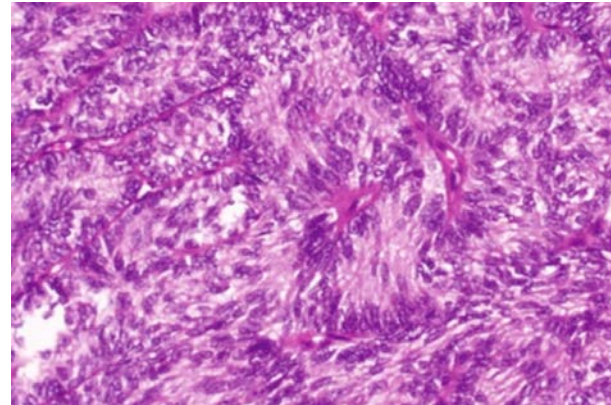
Correct diagnosis

- AGCT presents with a wide range of different histologies
 - AGCT is rare; diagnosis can be difficult for even experienced pathologist
 - **20-40% false diagnosis** in historical series (*Cronje et al 1999, Bryk et al 2015*)
- FOXL2 402 C-> G mutation is specific to AGCTs
 - Easily feasible assay
 - DNA from diagnostic samples (FFPE)
 - qPCR-based TagMan Allelic Discrimination
 - Validated for clinical use in difficult cases (*Kommoss et al, 2013*)

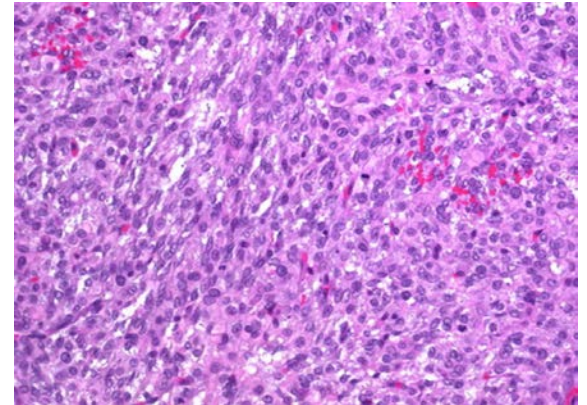
Microfollicular



Trabecular

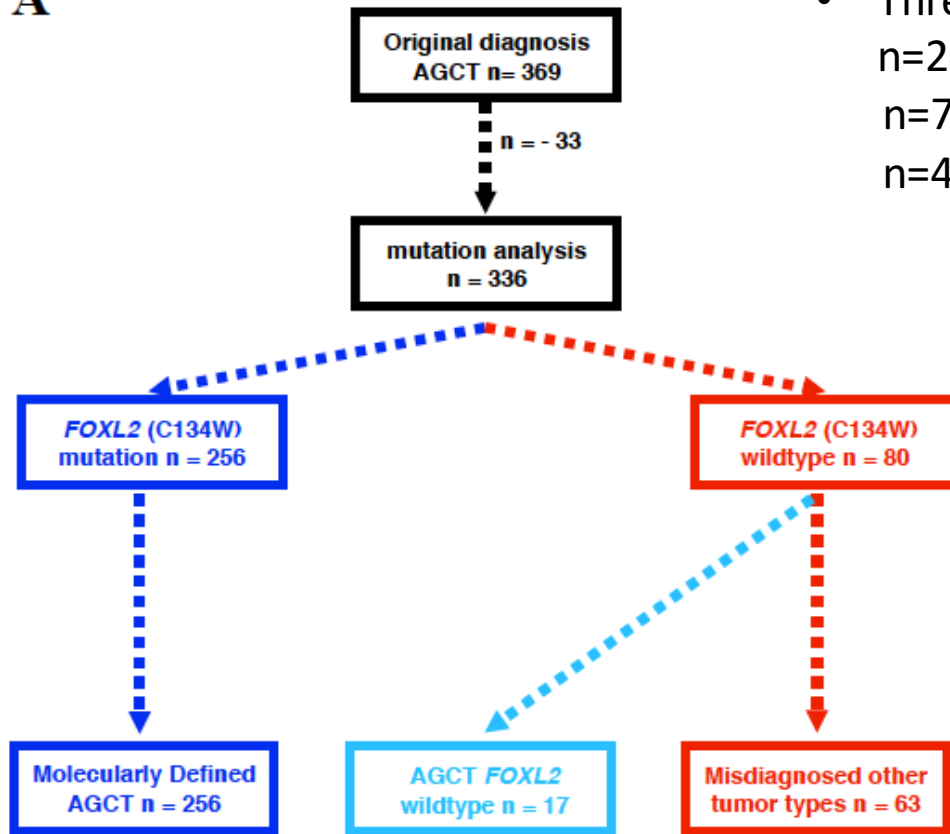


Undifferentiated



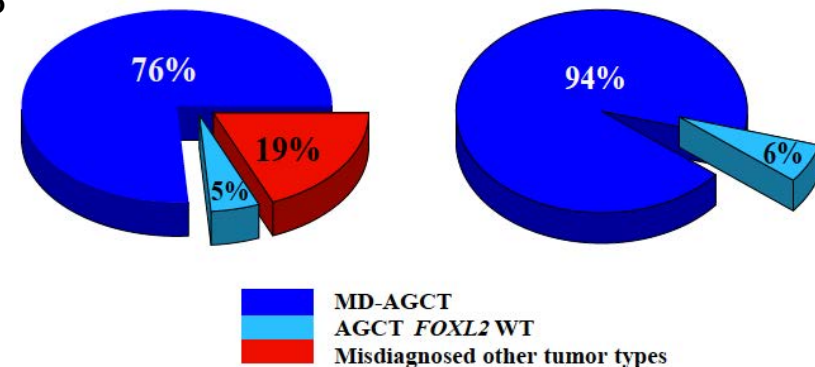
Effect of molecular diagnosis on outcomes?

A



- Three cohorts;
n=248 Helsinki, Finland
n=79 Amsterdam, the Netherlands
n=42 Tübingen, Germany

B



Misdiagnosed tumors

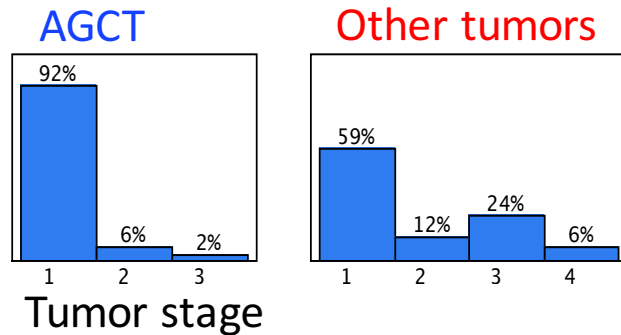
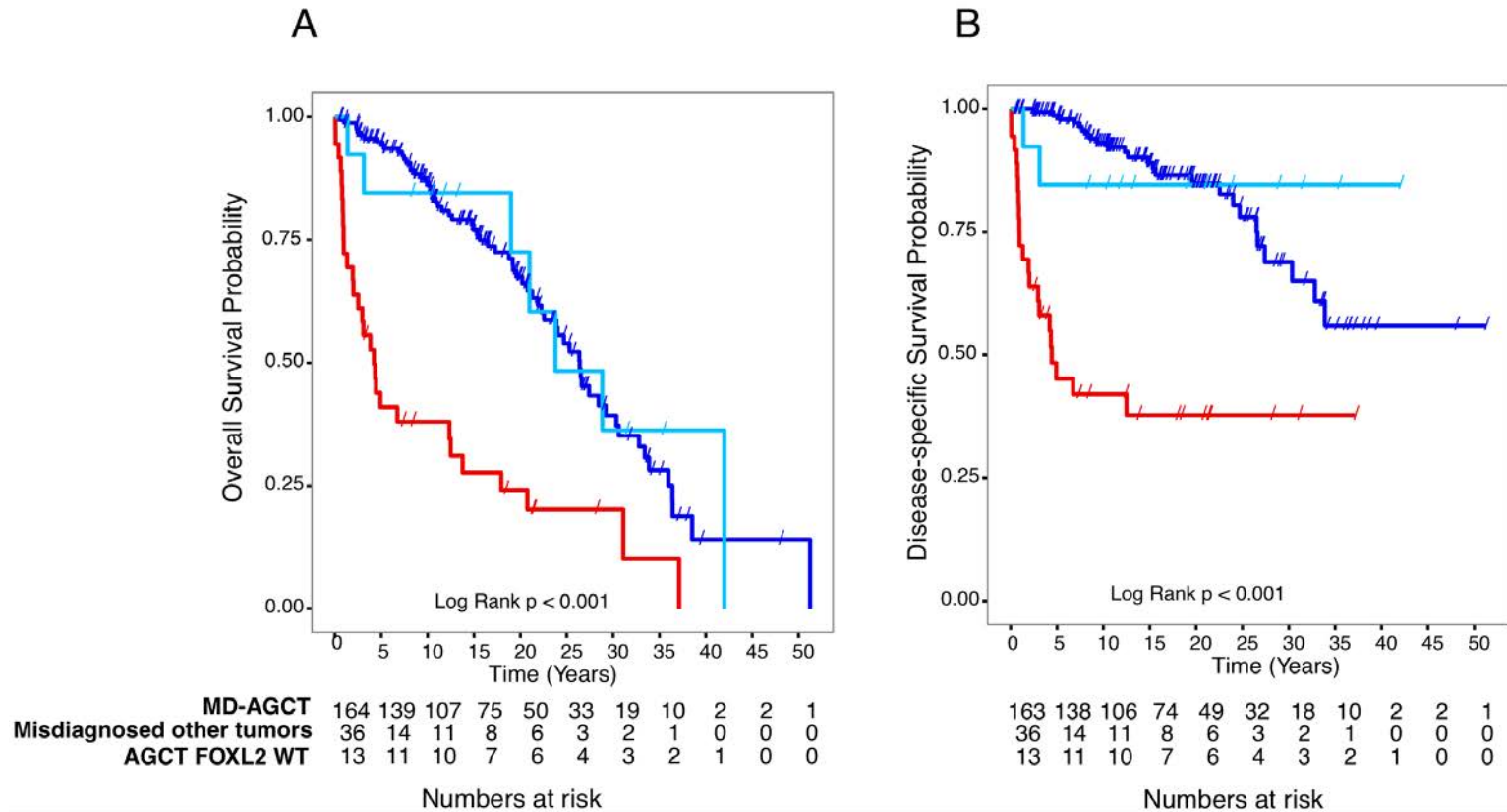


Table 2 Histology of FOXL2 wt tumors after final review		n (%)
Ovarian carcinoma		17 (29)
aGCT FOXL2 wild-type		12 (21)
Seroid cell tumor		4 (7)
Thecoma		4 (7)
Metastatic carcinoma		3 (5)
Sertoli-Leydig cell tumor		3 (5)
Sex cord stromal tumor with annular tubules		3 (5)
Fibroma		2 (4)
Brenner tumor		1 (2)
Cellular Fibroma		1 (2)
Juvenile GCT		1 (2)
FATWO*		1 (2)
Sex cord stromal tumor		1 (2)
Transitocellular carcinoma		1 (2)
ND		3 (5)
Total		57
* Female Adnexal Tumor of probable Wolffian Origin		

(Mc Conechy et al JNCI, In press)

Outcomes

AGCT
AGCT – FOXL2 wt
Misdiagnosed tumors



(Mc Conechy et al JNCI, In press)

Survival

Follow-up Time	
Reverse KM	10.49
OS % (95%CI)	
5-year	93.3 (91.5-98.4)
10-year	84.4 (79.5-89.5)
15-year	72.1 (65.6-79.2)
Deaths	
Yes	92 (35.9%)
No	164 (64.1%)
DSS % (95%CI)	
5-year	97.4 (95.3-99.5)
10-year	91.8 (88.0-95.8)
15-year	85.4 (80.0-91.2)
Deaths of Disease	
Yes	42 (16.4%)
No	213 (83.2%)
Unknown	1 (0.4%)

By stage

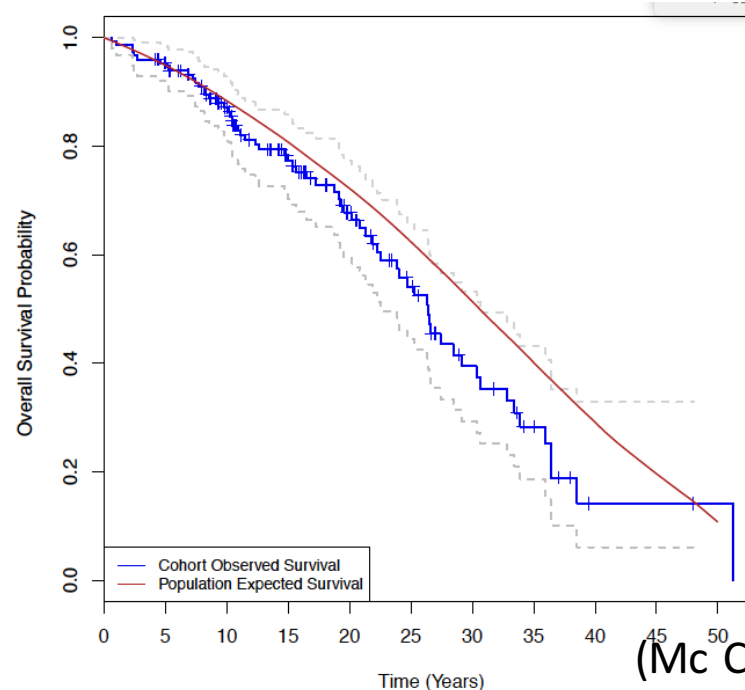
Overall survival			
Stage	5-year	10-year	15 year
Ia	97,6	93,3	88,1
Ic	92,0	87,3	76,1
II-III	92,3	61,5	52,7

Disease Specific Survival			
Stage	5-year	10-year	15 year
Ia	100	97,1	95,1
Ic	97,8	92,8	86,4
II-III	100	74,1	63,5

(Mc Conechy et al JNCI, In press)

AGCT survival compared to general population

- 165 Verified AGCT patients from Helsinki, Finland (Blue crosses)
- Life expectancies of age, gender and year – matched general population from Finland (Red line)



(Mc Conechy et al JNCI, In press)

AGCT relapses

Number of Patients with Recurrent Disease

Yes	90 (35.2%)
No	143 (55.9%)
Unknown	23 (9.0%)

% Relapsed by Age and Stage

Age Grp	Stage Ia		Stage Ic	
	No Recurrence	Recurred	No Recurrence	Recurred
< 50	27 (58.7%)	19 (41.3%)	12 (41.4%)	17 (58.6%)
51-65	44 (88.0%)	6 (12.0%)	17 (53.1%)	15 (46.9%)
65	9 (75.0%)	3 (25.0%)	5 (55.6%)	4 (44.4%)

% NOT Relapsed by Stage

RFS			
Stage	5-year	10-year	15 year
Ia	93,7	80,2	76,2
Ic	84,8	63,6	40,7
II-III	88,9	53,3	53,3

High-risk; Stage Ic
<50 years
Low-risk; >50 years
AND stage Ia

Time to relapse

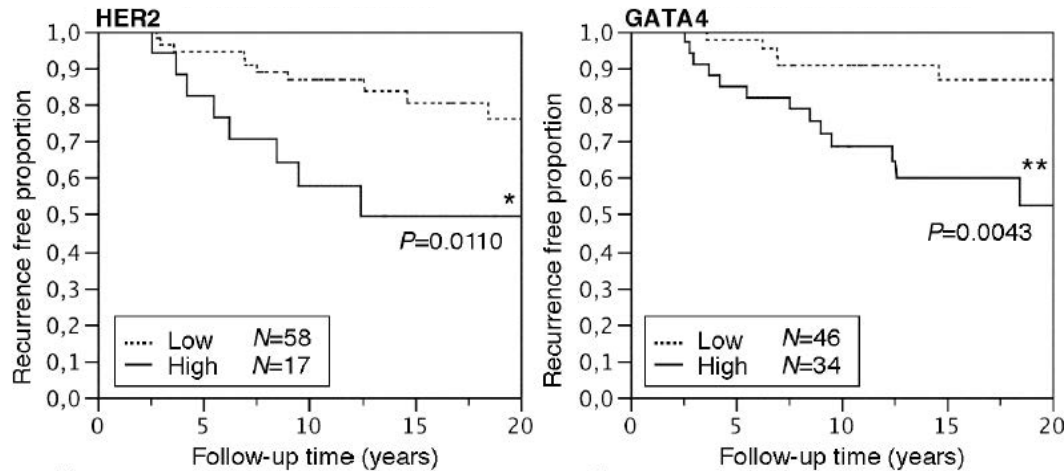
Median time to relapse; 7.2 years
Range; 1 - 27 years

Relapses 33% within 5 years
78% within 10 years
95% within 15 years

*(Mc Coneghy et al, 2016,
Farkkila et al, 2014)*

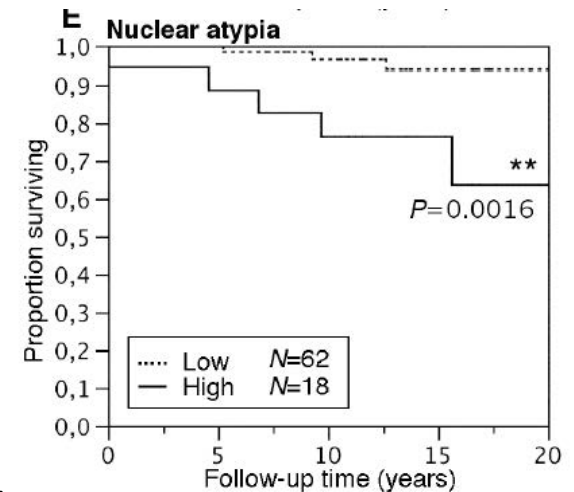
Prognostic factors

A Disease-free survival



Factor	Stage I HR (95% CI) p-value	Stage Ia HR (95% CI), p-value
GATA4	4.99 (1.14-34.21), 0.0322	7.71 (1.12-151.85), 0.0375

B Disease specific survival



(Färkkilä et al, 2014)

When and How to follow-up?

International guidelines:

USA; National Comprehensive Cancer Network (NCCN)

Europe; European Society of Medical Oncology (ESMO)

- Follow-up scheme
 - First 2 years; every 2-4 months
 - 2-5 years; every 6 months
 - > 5 years; yearly, until progression
- Examinations
 - History
 - Physical & pelvic exam
 - Tumor markers; Inhibin suggested
 - Ultrasound if the other ovary has not been removed (every 6 months)
 - CT scan only when necessary

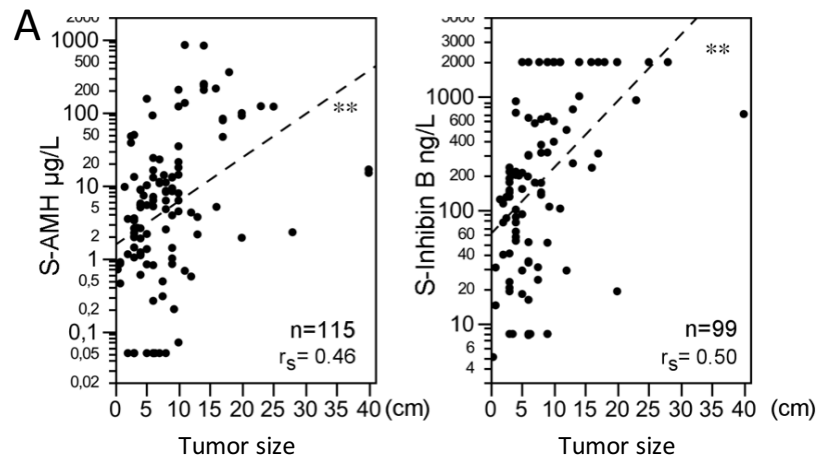
Follow-up marker

Inhibin B is the current marker

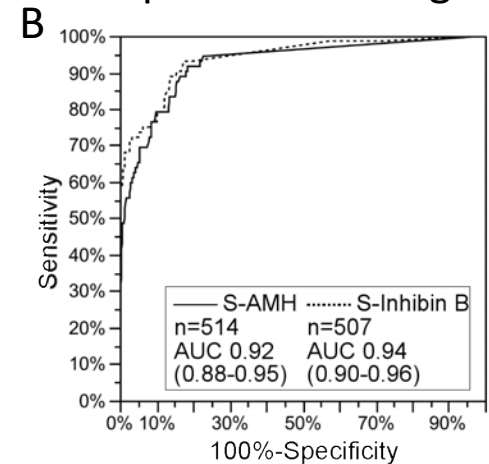
- Significantly superior to Inhibin (total) or Inhibin A (*Mom 2007*)
- Fluctuates during menstrual cycle
- 10-15% AGCTs are Inhibin B negative

Anti-Müllerian Hormone (AMH)

- AMH and Inhibin B positively correlate to tumor size



AMH and Inhibin B
Are equal in detecting AGCT



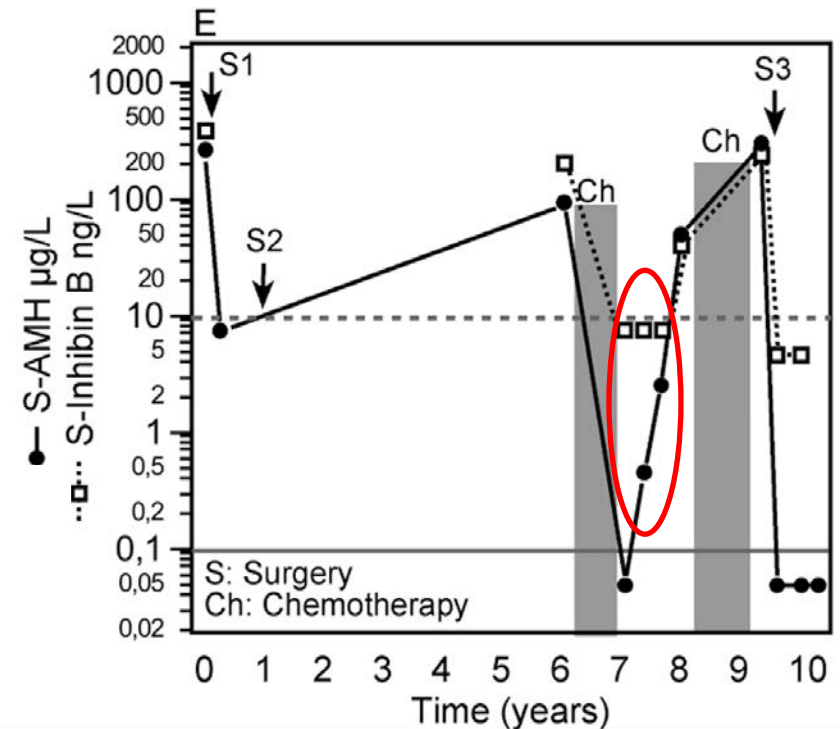
(Färkkilä et al, 2015)

AMH and Inhibin B are highly sensitive and specific

	Sensitivity	Specificity
AMH	92%	82%
Inhibin B	93%	83%

Combination of AMH and Inhibin B is superior to inhibin B alone

All samples (n=514)	
AMH	0.92 (0.88-0.95)
<u>InhB</u>	0.94 (0.90-0.96)
Combined	0.95 (0.91 -0.97) *0.03 (InhB)



Lead times; 3,4 years for AMH
2.8 years for Inhibin B

(Färkkilä et al, 2015)

Optimal follow-up?

1. **Correct diagnosis**
 - FOXL2 mutation assay should be performed to all AGCT suspicions
2. **Identification of high-risk patients**
 - Stage Ic, or tumor rupture
 - < 50 years
3. **Follow-up Scheme**
 - Only 1/3 of the relapses come within the first 5 years
 - Median time to relapse 7-8 years
 - **Yearly follow-ups for up to 15 (20) years?** At least in high risk patients.
 - **Mammography!** – increased risk of breast cancer; 1-20% (*Ohel 1983*), 3.3x (*Hammer 2013*)
 - **Endometrial assessment** (ultrasound/biopsy) if uterus was not removed
4. **AMH and Inhibin B are sensitive and specific serum markers**
 - Evaluation of both markers at diagnosis
 - Combination or Inibini B alone to be utilized during follow-up
5. **New studies are needed to evaluate the effect of follow-up on survival, morbidity and quality of life!**

Thank you!

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TRAIL is a promising target for therapy in AGCTs

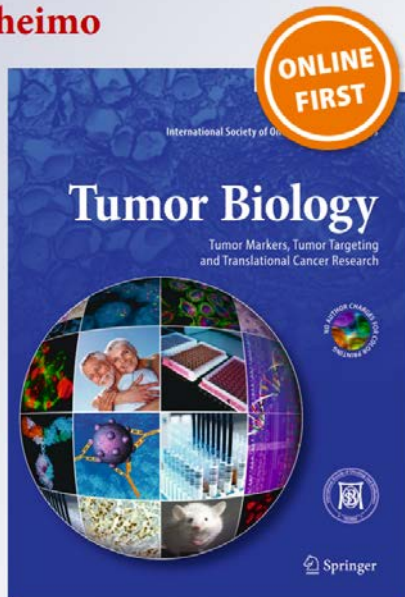
Circulating levels of TNF-related apoptosis inducing-ligand are decreased in patients with large adult-type granulosa cell tumors —implications for therapeutic potential

Anniina Färkkilä, Giorgio Zauli, Ulla-Maija Haltia, Marjut Pihlajoki, Leila Unkila-Kallio, Paola Secchiero & Markku Heikinheimo

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